PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Community-based Exercise for Health Promotion and Secondary Cancer Prevention in Canada: Protocol for a Hybrid Effectiveness-Implementation Study
AUTHORS	McNeely, Margaret; Sellar, Christopher; Williamson, Tanya; Shea-Budgell, Melissa; Joy, Anil Abraham; Lau, Harold; Easaw, Jacob; Murtha, Albert; Vallance, Jeffrey; Courneya, Kerry; Mackey, John; Parliament, Matt; Culos-Reed, Nicole

VERSION 1 – REVIEW

REVIEWER	Michael P Foley Idaho State University, USA
REVIEW RETURNED	24-Mar-2019

GENERAL COMMENTS	The reviewer provided a marked copy with additional comments. Please contact the publisher for full details.

REVIEWER	Nora Nock Case Western Reserve University Cleveland, OH, USA
REVIEW RETURNED	16-Apr-2019

GENERAL COMMENTS	This manuscript describes the protocol for a hybrid effectiveness-implementation community-based exercise program in cancer survivors taking place in Canada. It is important to disseminate the information about this trial that is now underway; however, there are several concerns with the manuscript in its current state. In general, there are some very important aspects of the protocol missing including, but not limited to, the exercise intervention goals and components. Below, is a summary of the concerns and missing information that should be provided by section: ABSTRACT: - the start and end dates should be added; -the number of community sites by type of site (e..g, YMCA, academic institution) should be stated - what is "dose" (frequency, duration, intensity) of the 12-week program and what comprises (& who will be offered) the 12-week booster session? what is the target # minutes/week and intensity of activity? - what is the primary outcome? - who is funding this program? - follow-up at 1 year will not provide "long-term effectiveness" INTRODUCTION: - it is unclear what the "gap" is that this work will fill

	- add the current number of cancer survivors and the estimated numbers anticipated in the next decade - add discussion about the short and long term side effects ("late effects") of cancer treatments (physiological & psychological) and how exercise can help alleviate these symptoms - add discussion regarding the decrease in physical activity and fitness in cancer survivors after treatment compared to prior to treatment - add discussion of some prior trials that have evaluated effectivenss (& implementation) of exercise programs in the community; provide summary effect estimates on important outcomes OBJECTIVE: - add the primary outcome in Objective #1 - how/where will cost be evaluated - will formative work be used in Objective #3? METHODS: - clarify the total sample size & characteristics of the cancer population; clarify that this will include cancer patients during and after primary treatment - add a study schema - add details of the community settings; how many locations of the different types (YMCAs; academic institutions, etc.); add geographic coverage (a map could be particularly helpful) - clarify early in the section that the CEP is responsible for screening & add who the CEPs will report to; how many CEPs will be on the project? provide comment on the sustainability of this model (using CEPs paid for by the grant?) in Discussion - clarify what "safety issues" would result in exclusion; - there is mention of a "fitness test" in several places including in the screening; however, it is not listed in the measures; thus, clarify if the fitness testing is a cardiopulmonary stress test (CPX) or is this a pseudo-measure of fitness via the 6 MWT? what are the specific inclusion/exclusion criteria for this test? - it would be helpful to have a reference or website link for the CEP certification program - unclear how /which screening will be performed "online" and "via phone" - unclear how the community stakeholders (not just patients) have contributed to the "design" of the program; were focus groups completed? where are those results? - the details of the exercise programs are missing! what is the exercise "dose"? will everyone get the same prescription? what is the target min/week and at what intensity? (eg 150 min/wk at moderate intensity)? & how will this be tracked? - the referral process & definition of "high needs" needs better described - add references for the various measures & discuss reliability and validity oft he measures in cancer survivors - unclear why all the tests cannot be performed in all locations - how will safety issues (adverse events) be tracked & reported - define "RE-AIM" at first use - will the controls also be matched on "gender"? - unclear exactly how cost / cost effectiveness will be measured and evaluated - how will intervention fidelity be measured? - the section on statistical power needs clarification; if the trial only needs 161 patients to meet 80% power for the estimated effect

	size of the primary outcome at 1 year compared to baseline, why are investigators planning to conduct the trial on 2500 patients? the expected effect sizes and "MID" need better justified; the oversampling of certain tumor types should be discussed in patient recruitment/study population DISCUSSION: - the label for this section is missing - add discussion on what this study will add to other completed and ongoing hybrid effectiveness-implementation exercise trials

VERSION 1 – AUTHOR RESPONSE

Reviewer 1:

- Please consider how referrals will be made

We have added more information on referrals (Page 6: last paragraph).

- Consider defining other patient reported outcomes and utilizing accepted outcome measures for physical function.

We appreciate this suggestion. As the study was both funded (and has started) using the proposed outcomes, we are not able to make changes at this point. Please note that the proposed outcomes were chosen in discussion with our stakeholders and as they align with other programming within our province in the Chronic Disease area.

- Consider screening patients for physical function e.g. balance assessment, grip strength, TUG and utilizing these measures for referral.

We appreciate this suggestion and agree with the reviewer. Our screening is done electronically due to the large number of sites and potential participants. Patients can self-refer to the program or their healthcare provider can refer them. Study staff do not attend the oncology clinics. Balance, grip strength and sit-to-stand are part of our objective outcome measures but are not evaluated in clinic for referral purposes.

- please clarify "have existing long-term or late presenting effects of their cancer treatment"

We have added more information on long-term and late presenting effects (Page 7: paragraph 4).

- Please clarify certified EP and what training and experience in cancer field means

We have added further information on the CEP credentials (Page 7; last paragraph).

- What are the baseline physical fitness tests and how are they evaluated?

The baseline fitness tests are our objective outcomes. We have revised using consistent terminology throughout the manuscript.

- Geographic location? Pt. choices?

Yes, choice of programming based on location is at the discretion of the patient assuming no safety issues have been identified. We have added further information in the text to clarify (Page 8; paragraph 1: added “location preferences”).

- Is the exercise specialist same as certified EP? Please define what an exercise specialist is.

No, the CEP has at minimum a University degree in Kinesiology as well as either post-graduate certification in exercise physiology or a Master’s degree in exercise physiology. The exercise specialist may be a graduate of a kinesiology program or college level personal training program. We have added further information to clarify the difference (Page 8; paragraph 2).

- Consider providing information regarding the Exercise: Training for Fitness Professionals

We have added further information on our cancer-specific education (Page 8 last paragraph).

- Please clarify who is making the referrals and what criteria are they using.

Patients can self-refer to the program or be referred by their healthcare provider. We have added further information to clarify the referral process (Page 6; paragraph 3).

- I understand the exercise modes may vary, however will there be parameters for exercise prescription? FITT-VP? This information is necessary for assessing effectiveness.

The class structure is standardized for the circuit-training program and for the group personal training sessions. The workload is set at an equivalent to approximately 8 MET hours per week; progressing to 10 MET hours per week by the end of the program. Participants report the time and intensity (perceived exertion) of exercise sessions in their diary and/ or training log (Page 9; last paragraph).

- Please consider stating the outcome measures and psychometrics for these measures.

We have added references to support validity and reliability in the text (Page 10-11).

- BMI is not an ideal method for health measure. Waist to hip ratio? or better outcome.

We agree with the reviewer. Of note, waist and hip measurements are also taken as objective outcome measures. We have revised the text as indicated (Page 10; added waist and hip circumference to the list).

- 6-MWT is not the best surrogate for aerobic fitness.

We agree with the reviewer. We have removed the classification.

Musculoskeletal fitness: grip strength, timed sit-to-stand, shoulder flexion (flexibility) and one-legged stance (balance);

- These measures are not necessarily msk fitness, e.g. balance is neuromuscular additionally consider providing rationale and psychometrics for the outcome measures (throughout).

Thank you. We agree with your comments. We have removed the classification.

- Adverse events… How will these be assessed? Consider having physical therapist or licensed professional assess these and how they will affect subsequent triage for care or resumption of exercise programming.

Thank you for this comment. We do have a medical advisor for the overall study, as well as Cancer Rehabilitation Services (physical and occupational therapy) within our cancer centres. Thus, as appropriate, participants can be seen and assessed. We have added further information as requested (Page 11, last paragraph)

- Will data be assessed for normality?

Yes. A statement to reflect the analyses has been added (Page 13; last paragraph).

- Effect sizes? MCID? MDC?

We have added further information to TABLE 1 as requested.

- Will there be any assessment of intra and interrelated reliability?

We will not be performing formal intra and inter-rated reliability due to the number of sites involved and the large geographical area. All testers are trained – and measurements are repeated where possible to optimize accuracy and reliability. Testing teams (including the two CEPs) from the Tertiary sites travel to the smaller cities in the north and south respectively to conduct the testing (Page 10; last paragraph).

- Many of these outcomes are different than ones listed in text. Consider utilizing MCID for differences (showing research)

Thank you for this comment. In TABLE 1: we have included measures of interest for the evaluation of effectiveness. We are also collecting other standard outcomes such as height and weight where we are not anticipating any changes/ impact from our program; however, these measures are standard to our protocol and will also be evaluated.

Reviewer 2:

ABSTRACT:
- the start and end dates should be added

Thank you. We have added the dates as requested.

-the number of community sites by type of site (e..g, YMCA, academic institution) should be stated

Thank you. We have added the number of sites by type.

- what is "dose" (frequency, duration, intensity) of the 12-week program and what comprises (& who will be offered) the 12-week booster session?

Thank you. We have added information on the exercise prescription.

what is the target # minutes/week and intensity of activity?

Thank you. We have added information on the minutes/week and intensity of activity.

- what is the primary outcome?

Please note, as this is a hybrid effectiveness-implementation study, we have two primary outcomes: one related to effectiveness which is related to physical activity levels at one year; and the other related to implementation: program reach, effectiveness, adoption, implementation and maintenance. This hybrid type design is better suited to evaluate community-based relevant research.

- who is funding this program?

We have added information on the funding agencies supporting the study.

- follow-up at 1 year will not provide "long-term effectiveness"

We agree with the reviewer's concern. Participants have the option to continue with follow-up questionnaires for at year 2 and 3 following the study. We have added further information to describe our plans for long-term evaluation of outcomes beyond the funding period.

INTRODUCTION:
- it is unclear what the "gap" is that this work will fill

Healthcare providers often advise cancer patients/survivors to adopt a more active lifestyle, yet few programs exist to support patients to make the prescribed behaviour change. Our proposed study is seen as a step towards bridging this gap. Moreover, we aim to address the limitations of prior implementation studies by paying closer attention to key effectiveness and implementation outcomes. We have revised the section to better reflect the identified gap (Page 5; last paragraph).

- add the current number of cancer survivors and the estimated numbers anticipated in the next decade

We have added this information as requested (Page 4; first paragraph).

- add discussion about the short and long term side effects ("late effects") of cancer treatments (physiological & psychological) and how exercise can help alleviate these symptoms

We have added this information as requested (Page 4; second paragraph).

- add discussion regarding the decrease in physical activity and fitness in cancer survivors after treatment compared to prior to treatment

We have added this information as requested (Page 4; second paragraph).

- add discussion of some prior trials that have evaluated effectivenss (& implementation) of exercise programs in the community; provide summary effect estimates on important outcomes

We have added this information as requested (Page 5: first paragraph).

OBJECTIVE:
- add the primary outcome in Objective #1

We have added this information as requested (Page 6; first paragraph).

- how/where will cost be evaluated.

Further details are provided on Page 12 section: Healthcare Utilization.

- will formative work be used in Objective #3?

Yes, we will use formal and informal methods of assessment to inform and improve processes. We have further detail to this section to explain (Page 6; objective 3).

METHODS:

- clarify the total sample size & characteristics of the cancer population; clarify that this will include cancer patients during and after primary treatment

We have added this information as requested (Page 6 last paragraph).

- add a study schema
We have added a study schema as requested (Figure 1).
- add details of the community settings; how many locations of the different types (YMCAs; academic institutions, etc.); add geographic coverage (a map could be particularly helpful)
We have added a map as suggested (Figure 2).

- clarify early in the section that the CEP is responsible for screening & add who the CEPs will report to; how many CEPs will be on the project?

We have added this information as requested (Page 7 last sentence; page 8; first paragraph).

- clarify what "safety issues" would result in exclusion;

We have added this information as requested (Page 8; paragraph 1).

- there is mention of a "fitness test" in several places including in the screening; however, it is not listed in the measures; thus, clarify if the fitness testing is a cardiopulmonary stress test (CPX) or is this a pseudo-measure of fitness via the 6 MWT? what are the specific inclusion/exclusion criteria for this test?

The fitness test reflects testing of our objective outcomes. All screening is done prior to baseline testing – for both exercise testing and training. We have removed the term “fitness test” to avoid confusion.

- it would be helpful to have a reference or website link for the CEP certification program

We have added this information as requested (Page 7; last paragraph).

- unclear how /which screening will be performed "online" and "via phone"

We have added this information as requested (Page 8; paragraph 2).

- unclear how the community stakeholders (not just patients) have contributed to the "design" of the program; were focus groups completed? where are those results?

Stakeholders, including survivors, were included from the time of inception of the ACE study design, and provided input on the grant application. Focus groups were also conducted with patients through and following pilot testing of the program. Details related to focus group work have not been published to date. (Page 9; Patient and stakeholder engagement)

- the details of the exercise programs are missing! what is the exercise "dose"? will everyone get the same prescription? what is the target min/week and at what intensity? (eg 150 min/wk at moderate intensity)? & how will this be tracked?

We have added further information to clarify (Page 9-10).

- the referral process & definition of "high needs" needs better described

We have added further information to clarify (Page10; paragraph 2).

- add references for the various measures & discuss reliability and validity oft he measures in cancer survivors

We have added this information to the section.

- unclear why all the tests cannot be performed in all locations

Not all sites have the time, space and equipment in place to perform all tests. Thus, for the purposes of implementation and to allow for program adoption across sites, some tests are optional. This way, each site can tailor the program to their local context (Page11; paragraph 2).

- how will safety issues (adverse events) be tracked & reported

We have added first further information on adverse events (Page 11; last paragraph).

- define "RE-AIM" at first use

Thank you. We have provided a definition (Page 12; paragraph 1).

- will the controls also be matched on "gender"?

Thank you. Yes, they will be matched on biological sex. This has been added (Page 12; paragraph 2).

- unclear exactly how cost / cost effectiveness will be measured and evaluated

As we have a public healthcare system, costs will be calculated as associated with health service type code and category, physician claims data, emergency room visits, and hospitalizations (Page 12; paragraph 2).

- how will intervention fidelity be measured?
Thank you for this comment. We have added further information to clarify (Page 10, Paragraph 1).

- the section on statistical power needs clarification; if the trial only needs 161 patients to meet 80% power for the estimated effect size of the primary outcome at 1 year compared to baseline, why are investigators planning to conduct the trial on 2500 patients?

The sample size largely reflects the implementation focus of the study (capacity building) rather than the power needed for statistical analyses. We have revised this section to reflect a more conservative approach to our sample size. We realize we will be overpowered for our primary outcomes; however, the larger sample size will allow for subgroup analyses.

-the expected effect sizes and "MID" need better justified;

We have added further information in Table 1.

- the oversampling of certain tumor types should be discussed in patient recruitment/study population

Thank you. We have moved this information as suggested (Page 7; paragraph 2).

DISCUSSION:

- the label for this section is missing

Thank you. We have added the label.

- add discussion on what this study will add to other completed and ongoing hybrid effectiveness-implementation exercise trials

Thank you. We have added further information throughout the discussion (Page 14-15).

-provide comment on the sustainability of this model (using CEPs paid for by the grant?) in Discussion

We have added information on the sustainability of CEPs within the model (Page 16; paragraph 1).

VERSION 2 – REVIEW

REVIEWER	Michael Foley Department of Physical and Occupational Therapy Idaho State University Pocatello, Idaho 83209-8045, USA
REVIEW RETURNED	24-Jul-2019

GENERAL COMMENTS	This manuscript significantly improved with this considerably revision. Well done. Thank you for addressing my comments. I believe most have been addressed adequately. Please consider the following comment on the FITT-VP parameters: " Exercise Intervention" page 50/70 pdf proof paragraph one you state "Participants take part in a combination of aerobic, resistance, balance, and flexibility exercises delivered in a standardized circuit-type class setting or group personal training format, twice

	weekly for a minimum of 60 minutes per session (approximately 3-4 metabolic equivalent units per session) for a 12-week period." I am not clear on the 3-4 metabolic equivalent units per session. In your response letter, you state "The class structure is standardized for the circuit-training program and for the group personal training sessions. The workload is set at an equivalent to approximately 8 MET hours per week; progressing to 10 MET hours per week by the end of the program. Participants report the time and intensity (perceived exertion) of exercise sessions in their diary and/ or training log (Page 9; last paragraph). My question 3-4 MET x 60 minutes per session this would be 180 - 240 MET-minutes per session time two sessions = 360-480 MET-min/week. I think further clarification with commonly reported terms would be helpful. I commend your efforts and contributions towards helping cancer survivors reduce morbidity.

VERSION 2 – AUTHOR RESPONSE

Reviewer 1: My question 3-4 MET x 60 minutes per session this would be 180 - 240 MET-minutes per session time two sessions = 360-480 MET-min/week.

I think further clarification with commonly reported terms would be helpful.

Response: We have provided further clarification (as per below) in the manuscript as requested by providing the MET equivalent in minutes (versus hours) and by providing an analogy to walking that may be more easily understood by readers.

"The program includes options for low-to-moderate intensity exercise set at 3 to 4 metabolic equivalent (MET) units per session (360-480 MET-minutes per week) and is progressed in intensity to 4 to 5 METs over the 12-week program duration (480-600 MET-minutes per week) as a means to progress participants towards recommended physical activity levels (500-1000 MET-minutes per week).31 In terms of intensity, this would be similar to prescribing walking at a comfortable pace (4 km per hour) initially and then slowly progressing to a brisk walking pace (6 km per hour) over a 12-week period."

We hope this revision addresses the concern of the reviewer.

VERSION 3 – REVIEW

REVIEWER	Michael Foley Department of Physical and Occupational Therapy Idaho State University, Pocatello, Idaho, USA
REVIEW RETURNED	16-Aug-2019

GENERAL COMMENTS	Thank you for your clarification, well done.